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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/287,573	04/06/99	WALT D	A67207-2/DJB

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EXAMINER	
GABEL, G	
ART UNIT	**PAPER NUMBER**
1641	14

DATE MAILED: 02/27/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Offic Action Summary	Application No. 09/287,573	Applicant(s) WALT ET AL.	
	Examiner Gailene R. Gabel	Art Unit 1641	

-- The MAILING DATE of this communication appears on the cover sh et with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

1)☒ Responsive to communication(s) filed on *17 January 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-44* is/are pending in the application.

4a) Of the above claim(s) *1-15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claims *1-44* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of the CERTIFIED copies of the priority documents have been:

1.☐ received.

2.☐ received in Application No. (Series Code / Serial Number) _____ .

3.☐ received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

14) ☐ Notice of References Cited (PTO-892)
15) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
16) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
17) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
18) ☐ Notice of Informal Patent Application (PTO-152)
19) ☐ Other: .

DETAILED ACTION

Continued Prosecution Application

1. The request filed on 1/17/01 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/287,573 is acceptable and a CPA has been established. An action on the CPA follows. Applicant elected Group III, claims 16-26 and added claims 27-44 in Paper No. 10. Claims 1-15 have been withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention. Currently, claims 16-44 are pending and under examination.

Priority

2. It is noted that this application claims priority to copending Application No. 08/944,850 filed October 6, 1997 and PCT/US98/21193 filed October 6, 1998 as stated in the first line of the specification. However, the current status of the nonprovisional parent applications referenced should also be included.

Drawings

3. This application has been filed with informal drawings which are acceptable for examination purposes only. The drawings in this application are also objected to by the Draftsperson (see PTO-948 attached). Correction is required. However, formal correction of noted defect can be deferred until application is allowed by the examiner.

Specification

4. Throughout the specification, the characters "A" and "@" are mediated by specific technical or otherwise, terms used by the Applicants.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 16-44 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 16 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. Claim 16 is indefinite and confusing in reciting "performing a statistical analysis on said measurements" because it is unclear which specific "measurements" are being statistically analyzed especially upon inclusion of step b). Specifically, claim 16 is unclear as to the structural cooperative relationships between the elements of the method steps, i.e. individual optical responses and sums, thereof. See also claims 25, 27, 34, 35, 36, 37.

Claim 16 is vague and indefinite in reciting "upon exposure to a target analyte" because it implies but not specifically, positively, and actively recite exposing the sensor

elements to a target analyte in the claim. See also claims 25 and 27. Further, it is unclear as to what applicants intend to encompass by reciting "target analyte" since in the specification, applicants appear to make reference to a "reference analyte". See page 40, line 1.

Claim 17 has improper antecedent basis problem in reciting "A method according to ...". Change to --The method according to ...-- for proper antecedent basis. See also claim 18.

Claim 17 is vague and indefinite in reciting "the baseline of at least one optical response

signature is adjusted" because it is unclear what is encompassed by the term "adjusted" and what particular parameter the "adjustment" is being based on. See also claim 26.

Claim 18 is indefinite confusing in reciting "ratio is increased by a factor of at least 10." because it is unclear as to how " the factor of at least 10" is increased, i.e. cumulatively, multiply (exponentially).

Claim 19 is indefinite confusing in reciting "analyte detection limit is reduced by a factor of at least 100" because it is unclear as to how " the factor of at least 100" is reduced, i.e. cumulatively, multiply (exponentially).

Claim 20 is vague and indefinite in reciting "sensor array comprises a population of beads dispersed on a substrate" because it is unclear as to what the relationship is between the "beads" in the instant claim and the "sensor elements" in claim 16 to which it depends upon, with respect to the sensor array.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claim 16 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

In this case, the specification does not appear to provide any literal support for the recitation of "method for increasing the signal-to-noise ratio in the characteristic optical response" in claim 16. Page 5, line 25 in the specification discloses "methods for reducing the signal-to-noise ratio in the characteristic optical response" . None of the originally filed claims recited the limitation in question. Recitation of claim limitation lacking literal support in the specification or originally filed claims constitutes new matter. Alternatively, if Applicants have support of such limitation in the specification, it is requested that it be specifically pointed out so as to obviate this pending rejection.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 16-17, 20-39, and 40-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Walt et al. (US 6,023,540).

Walt et al. disclose a sensor array system for use in measuring optical responses comprising a population of sensor elements or beads/microspheres with separate subpopulations of sensor elements therein, typically randomly distributed in an array across a fiber optic bundle end (see Abstract). By imaging the end of the bundle onto a CCD array, optical signatures of the microspheres are individually interrogatable. The system measures optical responses and monitors optical signature changes associated with the different subpopulations of sensor elements by coupling those changes into separate optical fibers or fiber optic bundles for transmission to the proximal end where statistical analysis is performed manually or automatically using image processing techniques. Specifically, Walt et al. disclose that each subpopulation of sensor elements carries a different chemical functionality, i.e. genosensors, and an optically interrogatable code descriptive of the chemical functionality (see column 8, lines 5-11, column 10 and column 13, lines 42-44). The presence of a target analyte is determined by a change in the optical signature as reflected after decoding the signature of the chemical functionality of the sensor element (see column 11, lines 1-14). In an experiment, Walt et al. selected a range of ratios representative of optical signatures for the dye ratio of a subpopulation based on the quantum yield of two dyes and the optical signature was obtained using the formula in column 13, lines 57-60. The sensor elements are encoded using dyes, i.e. fluorophores and chromophores, entrapped

within the elements in a specific ratio wherein fluorescent dyes are preferred due to their strong signal, thereby, providing good signal-to-noise ratio for decoding (see column 5, lines 20-52 and column 6, lines 53-59). If fluorescein background from a solution is too high to see the optical signal, the fiber optic bundle can be placed in a buffer to adjust the baseline of an optical response signature and remove background fluorescence (see column 15, lines 38-40). Additional encoding parameters include varying sizes of microspheres in order to expand the encoding dimensions (see column 13, lines 33-42). Although each sensor has different distribution of populations, only those with positive optical response or signature change is decoded, thereby, excluding all outlying beads. A computer executes image processing software to process the information from a CCD camera and measure/analyze optical responses of a plurality of subpopulations of sensor elements exposed to target analytes (see column 11, lines 51-54).

Walt et al. is silent in specifically teaching the step of summing the optical responses as well as the statistical analysis and calculations of data obtained from individual or combinatorial optical signal measurements from sensor elements such as the analytical requirements recited in instant claims 32-39. However, it would have been obvious to obtain a summation of optical responses of at least two sensor elements in a given subpopulation in a sensor array in order to establish a baseline optical response signature representative of the subpopulations. Further, statistical analysis strategies, i.e. calculating mean/average, standard deviation, precision/ repeatability of a method as reflected in a second analysis, confidence intervals,

correlation studies, and distribution/cluster analysis and evaluation are standard laboratory practice and a requirement in optimization procedures. Since Applicant has not disclosed that the specific limitations recited in instant claims 32-39 are for any particular purpose or solve any stated problem, absent unexpected results, it would have been obvious for one of ordinary skill to use statistical analysis strategies known and conventionally used in prior art.

8. Claims 16, 23-25, 27-30, and 32-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pinkel et al. (US 5,837,196).

Pinkel et al. disclose methods of performing quantitative analysis of biological molecules using a fiber optic biosensor. Pinkel et al. specifically disclose the fiber optic biosensor as comprising a high density array of sensor elements or bioactive agents (biological binding partners) which are uniquely addressed such as oligonucleotides, nucleic acids, and proteins and which are linked to a multiplicity of optical fibers bundled together (see column 3, lines 8-22 and column 4, lines 55-67). Pinkel et al. use a matrix solution for the attachment of the sensor elements into solid surface such as optic fibers and beads (see column 3, limes 37-38 and column 11, lines 50-55). Pinkel et al. also disclose that use of concave or convex sensor ends provides a greater surface area upon which to immobilize a bioactive agent thereby increasing the signal to noise ratio per optical fiber (efficiency) of the biosensor (see column 8, lines 22-25). Each optic fiber includes a sensor end and a transmission end, each one sensor end (a first and a

second sensor end, for example) having attached a bioactive agent wherein a transmission array having first and second positions addresses the transmission ends of the first and second fibers. An optical interrogation means is for use in examining the comparative attachment between a first and a second target analyte and the relative increase or decrease of the target analytes are also evaluated (see column 4, lines 35-50 and column 7, lines 14-15). In hybridization studies, the greater the ratio of signal intensities on an oligonucleotide probe, the greater the copy number ratio of sequences in two target analytes that bind the probe (see column 21, lines 17-29). A detector which focuses, detects, enhances or amplifies optical signals produced by binding reactions and conducted along respective optical fibers to a transmission end, also measures aggregate signals and transforms signals into digital or analog electrical signal (see column 3, lines 40-49 and column 9, lines 23-57). By examining the uniquely addressed transmission ends of fibers or groups of fibers, the addressed transmission ends can transmit unique patterns for rapid identification and measurement of analytes by the sensor (see column 4, lines 21-25). The detector system may also be equipped with a computerized data acquisition system and analytical program to provide a fully automated computer controlled analytical system wherein optical responses are measured, results are observed, and diverse parameters are statistically and concurrently analyzed and correlated (see column 13, lines 33-56). The detector may further be equipped with one or more filters to pass the emission wavelengths thereby increasing signal to noise ratio.

Pinkel et al. is silent in specifically teaching the step of summing the optical responses as well as the statistical analysis and calculations of data obtained from individual or combinatorial optical signal measurements from sensor elements such as the analytical requirements recited in instant claims 32-39. However, it would have been obvious to obtain a summation of optical responses of at least two sensor elements in a given subpopulation in a sensor array in order to establish a baseline optical response signature representative of the subpopulations. Further, statistical analysis strategies, i.e. calculating mean/average, standard deviation, precision/ repeatability of a method as reflected in a second analysis, confidence intervals, correlation studies, and distribution/cluster analysis and evaluation are standard laboratory practice and a requirement in optimization procedures. Since Applicant has not disclosed that the specific limitations recited in instant claims 32-39 are for any particular purpose or solve any stated problem, absent unexpected results, it would have been obvious for one of ordinary skill to use statistical analysis strategies known and conventionally used in prior art.

9. Claims 18 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Walt et al. (US 6,023,540) or Pinkel et al. (US 5,837,196).

Walt et al. and Pinkel et al. have been discussed supra. Walt et al. and Pinkel et al. fail to disclose increasing signal-to-noise ratio by a factor of at least 10 and reducing analyte detection limit by a factor of at least 100. However, it is maintained that

"increasing ... ratios by a factor" and "reducing ... detection limits by a factor" are all result effective variables which the prior art references have shown may be obtained via optimization procedures in order to achieve optimum results. The "discovery of an optimum value of a result effective variable in a known process is ordinarily within the skill of the art." Application of Boesch, 617 F.2d 272, 276, 205 USPQ 215, 218-219 (C.C.P.A. 1980). Therefore, one of ordinary skill in the art at the time of the instant invention would have reasonable expectation of success in obtaining such factors such as those in instant claims 18 and 19 using standard optimization procedures.

10. Claims 16, 25, 27, and 32-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rushbrook et al. (GB 2294319A).

Rushbrook et al. disclose detecting the position of a labeled material in a sample exposed to high density arrays of oligonucleotides which gives off optical signal by repetitively imaging the sample onto a CCD camera, scanning the CCD array, interrogating the charge pattern following each exposure, performing measurements on the data signals to obtain and identify clusters of data values, and comparing measurements with threshold to distinguish clusters resulting from optical signals from the remainder of a sample. Rushbrook et al. also disclose operating a visual display system so as to reproduce scanned area of the CCD array and adjusting baseline (modulating) the optical signal producing element in the display system in order to generate visually distinguishable features in the display. The sensitivity of the signal

processing and imaging analyzing system may be enhanced by optically coupling a sample to the photocathode of the image intensifier by means of a fiber optic coupling plate (see pages 3-5). Rushbrook et al. uses tapering (converging or diverging) fiber optic plates to achieve magnification or demagnification to the same extent as would be possible with a lens system with significantly less optical signal loss (see pages 16-18).

Rushbrook et al. is also silent in specifically teaching statistical analysis and calculations of data obtained from individual or combinatorial optical signal measurements from sensor elements such as the analytical requirements recited in instant claims 32-39. However, statistical analysis strategies, i.e. calculating mean/average, standard deviation, precision/repeatability of a method as reflected in a second analysis, confidence intervals, correlation studies, distribution analysis and evaluation are standard laboratory practice and a requirement in optimization procedures. Since Applicant has not disclosed that the specific limitations recited in instant claims 32-39 are for any particular purpose or solve any stated problem, absent unexpected results, it would have been obvious for one of ordinary skill to use statistical analysis strategies known and conventionally used in prior art.

11. For reasons aforementioned, no claims are allowed.

R marks

12. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Walt et al. (US 5,512,490) disclose optical sensing methods for detecting analytes of interest using spectral recognition patterns.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gailene R. Gabel whose telephone number is (703) 305-0807. The examiner can normally be reached on Monday to Friday from 7:00 AM to 4:30 PM. The examiner can also be reached on alternate Fridays at 7:00 AM to 3:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le, can be reached on (703) 305-3399. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

2/24/01

Gailene R. Gabel
Patent Examiner
Art Unit 1641

LONG V. LE
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

02/26/01